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(72) Inventors DIETRICH W. LÜBBERS and ALBERT HUCH

(19)

(54) METHOD AND DEVICE FOR DETERMINING THE PERFUSION EFFICIENCY FACTOR OF ANIMAL TISSUE

(71) We, L. ESCHWEILER & CO., a German Offene Handelgesellschaft, of 35, Holz Koppelweg, 2300 Kiel, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method and device for determining the perfusion efficiency factor of animal tissue.

The term "perfusion efficiency factor" as used herein is intended to designate a physiological value which is determined by the degree of perfusion of an indicator substance and the local concentration of the substance supplied to a given locus by the perfusion space surrounded by this first surface. It is also known to use other approaches, for instance to measure H_2 clearance as proposed by Lübbers, or to measure the radioactive clearance as proposed by Ingvar and Lassen.

Measurement of the indicator concentration at a given locus has also been proposed. For example, oxymetric measurements of the HbO_2 saturation in the capillary area of the skin have been proposed by Krammer, Huch, Lübbers and Wodick (HbO_2 represents oxygenated haemoglobin). Radioactive methods have also been proposed and there are a number of arrangements for measuring the concentration of blood gases which diffuse through the skin or the organ surface to an

PATENTS ACT 1949

SPECIFICATION NO 1461345

In accordance with the Decision of the Superintending Examiner, acting for the Comptroller-Gener dated 23 June 1981 this Specification has been amended under Section 14 in the following manner

Page 1, line 79, Page 5, line 3, *after* factor *insert* , said measurements being carried out utilis device comprising first means defining a surface adapted to be placed against the tissue to be measured; second means for producing a constant temperature at said surface; third means fc measuring the energy used to produce said constant temperature; and fourth means surround said surface for measuring the indicator concentration in said tissue
Page 2, line 2, Page 5, line 25, *after* tissue *insert* ; seventh means for comparing the tempera measured by said third and fifth means and for forming a signal indicating the difference bet said temperatures; and eighth means for combining said signal with a signal derived from said means to form a composite signal
Page 2, *delete* line 21 *insert* Patent Specification No. 1312, 169.
Page 3, line 1, *before* one *insert* part of
Page 3, lines 4 and 6, *after* illustrating *insert* part of
Page 3, line 12, *after* device *insert* in accordance with the invention
Page 5, line 22, *delete* and
Page 5, *delete* lines 56 to 60 and 66 to 73
Page 5, *for* claims 10 and 12 to 15 *read* 9 and 10 to 13
Page 5, line 81, *for* 12 *read* 10
Page 5, line 86, *for* 13 *read* 11
Page 5, *delete* lines 95 to 97 *insert* 14. A method according to claim 1 substantially as here-
Page 5, *delete* lines 100 to 103 *insert* 15. A device according to claim 3 substantially as here

THE PATENT OFFICE

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This invention relates to a method and device for determining the perfusion efficiency factor of animal tissue.

The term "perfusion efficiency factor" as used herein is intended to designate a physiological value which is determined by the degree of perfusion of an indicator substance and the local concentration of the substance supplied to a given locus by the perfusion. This factor may be determined by the relation:—

$$E=f(I.C),$$

where E is the perfusion efficiency factor, I is the rate of perfusion, and C is the indicator concentration.

In the case of organs, the rate of perfusion can be regarded as the rate of blood circulation in ml/unit weight/time.

Methods are already known for determination of the blood circulation of an organ at the surface thereof by measuring the thermal conductivity at the surface of the organ. This thermal conductivity depends upon the thermal conductivity of the tissue and the flow of blood through it, that is upon the rate of perfusion. This type of measurement was suggested by Gibbs in 1931 and was later improved by Hensel. It either measures the temperature difference between two thermal sensors of which one is maintained at a constant temperature, or two measuring surfaces are provided between which a constant temperature differential is produced and the amount of heat required to maintain the temperature differential is then measured. This latter approach was developed by Kanzow who utilises an annular diathermically heated surface, and a second measuring surface which is located at the centre of the space surrounded by this first surface. It is also known to use other approaches, for instance to measure H_2 clearance as proposed by Lübbers, or to measure the radioactive clearance as proposed by Ingvar and Lassen.

Measurement of the indicator concentration at a given locus has also been proposed. For example, oxymetric measurements of the HbO_2 saturation in the capillary area of the skin have been proposed by Krammer, Huch, Lübbers and Wodick (HbO_2 represents oxygenated haemoglobin). Radioactive methods have also been proposed and there are a number of arrangements for measuring the concentration of blood gases which diffuse through the skin or the organ surface to an electrode assembly.

However, known methods involve measurement of either the rate of perfusion or the indicator concentration but not both.

Thus, according to one aspect of the invention there is provided a method for determining the perfusion efficiency factor (as hereinbefore defined) of animal tissue, which comprises percutaneously measuring the rate of perfusion of an indicator substance in the tissue at a specified locus and simultaneously measuring the indicator concentration at said locus, signals being obtained in dependence on said measurements and the signals combined to obtain a composite signal corresponding to said factor.

According to another aspect of the invention, there is provided a device for use in the percutaneous measurement of the perfusion efficiency factor (as hereinbefore defined) of animal tissue, comprising first means defining a first surface adapted to be placed against the tissue to be measured; second means for producing a controlled temperature in said first means at said first surface; third means for measuring the temperature of said first surface; fourth means defining a second surface surrounded by and located substantially centrally of said first surface; fifth means for measuring the temperature of the tissue at said second surface; and sixth means also surrounded by

said first surface and operative for measuring an indicator concentration in said tissue.

A particularly important indicator for the local metabolic activity is oxygen and its pressure which is transported by the blood flowing through a tissue, the blood oxygen pressure being known as "blood-PO_2". Percutaneous measuring of blood-PO_2 is already known; however, methods known heretofore for this purpose have had the disadvantage that the skin-breathing effect is included in the measurements in a manner which is not controllable and which renders the measurements unreliable. For this reason, it has been proposed to so increase local blood circulation by applying maximum hyperthermia that the percutaneous blood-PO_2 approaches as much as is possible the arterial blood-PO_2. This has been proposed by Rooth and Baumberger and has been disclosed in German Patent Specification No. 2,145,400.

Hyperthermia normally causes a maximum enlargement of the blood vessels, so that the perfusion quantity is essentially determined by the blood pressure. However, experience has shown that—particularly in pathological cases—hyperthermia does not necessarily produce the desired maximum hyperemia. This means that a reduced percutaneous blood-PO_2 can occur even in the case of dilated blood vessels, as a result of a reduced O_2 entrance in the lung, as well as due to a reduced blood circulation.

To take this problem into account the present invention further proposes that, subsequently to measuring the perfusion efficiency factor, the blood circulation be locally interrupted, and, the rate of breathing of the skin be determined by measuring the blood-PO_2 pressure drop per unit of time (i.e. the value

$$\left(\frac{dPO_2}{dt}\right).$$

This has the advantage of eliminating the important potential source of the above-mentioned errors in measuring the perfusion efficiency factor.

To make this type of measurement possible the device includes an inflatable pressure-exerting cuff which permits localised interruption of blood circulation. This makes it possible to carry out the three measurements to be taken, namely measurement of the perfusion rate, measurement of the indicator concentration, and measurement of the rate of skin breathing, with a single piece of equipment and without having to change the measuring conditions, at least on those parts of the body—for instance the extremities such as the arms and the legs—where the cuff can be employed.

The device may also include an arrangement for making the temperature of the temperature measuring surfaces variable, so that said temperature can be raised beyond the skin temperature. This has the advantage that the non-linear behaviour of the skin breathing, and the dependency of the skin-PO_2 upon the temperature, can be taken into account in the measurements.

The invention also provides for the use of a first measuring surface on a component which is constructed as a counter electrode for platinum electrodes, and a concentration measuring device which is constructed as a multiple-wire platinum electrode. The electrode surfaces are in contact with an electrolyte and are covered by a gas-permeable membrane which is common to them.

The advantage of this arrangement is that it can be of light weight which eliminates the danger that the capillaries in the tissue might be squeezed shut and that the rate of perfusion might thus be unintentionally changed. Since it is an important requirement that the physiological conditions be changed as little as possible as a result of and during the measurements, contact between the apparatus and the tissue being investigated, particularly the contact pressure between them, is of considerable importance. If the contact pressure is too low, and the heat exchange is poor then, in the event that blood gases are used as the indicator, the leakage rate to the ambient atmosphere is so high that the indicator measurement is not reliable. This means that the measurements obtained cannot be used. If, on the other hand, the contact pressure is too great, then the capillary vessels will be squeezed shut and the perfusion rate will be varied in a manner which is neither controllable nor determinable.

To overcome these problems the first measuring surface may be annular and provided with an annular groove which is open at the surface that is to be placed against the tissue to be measured, and which can be connected to a vacuum pump. This has the advantage that the skin opposite the groove is drawn partly into the same by the suction effect existing in the groove. The contact pressure can readily be adjusted by selecting an appropriate width for the groove or by inserting supporting rings into the same. This type of arrangement is for instance suitable to carry out measurements under labour during childbirth. It is also possible to provide an adhesive layer on the measuring means, by means of which it can be readily and releasably secured to the tissue to be measured.

The invention will now be described by way of example with reference to the accompanying drawings which illustrate a number of embodiments of the invention and in which:—

Figure 1 is a diagrammatic illustration of

one embodiment of the invention, partly in section;

Figure 2 is a view similar to Figure 1, illustrating another embodiment of the invention;

Figure 3 is a perspective view illustrating a further embodiment of the invention;

Figure 3a shows the embodiment of Figure 3 applied to an arm;

Figure 4 is a circuit diagram, illustrating the connection of various components of a device;

Figure 5 is a view similar to Figure 4, illustrating an alternative arrangement; and

Figure 6 is a view similar to Figure 5, illustrating a still further arrangement.

Referring now firstly to the embodiment in Figure 1, it should be understood that this is intended for measuring the perfusion efficiency factor in cases where the indicator carried by the blood of the tissue being measured is of a radioactive nature. This might, for instance, be glucose which is provided with radioactive trace elements and has been injected into the bloodstream.

Reference numeral 10 designates an annular measuring surface of an annular member of a material having good thermal conductivity. The surface 10 is to be placed against a tissue or skin to be measured. The temperature of the surface 10 is measured by a thermal sensor 11 and can be varied by heating means (not shown in Figure 1), for instance an electrical resistance wire or the like as shown at 12 in Figure 2. A second measuring surface in Figure 1 is provided by a thermal sensor 13 which is located substantially at the centre of the annulus formed by the surface 10 and which serves to measure the temperature of the tissue itself. Arranged concentrically above the thermal sensor 13 is a measuring unit which measures the indicator concentration, for instance a counter tube 14 that is used to measure the concentration of a radioactively marked metabolically active substance (i.e., radioactively marked glucose) which is transported by perfusion through the tissue. The entire measuring means is accommodated in a housing 15 a surface of which faces in the same direction as the surface 10 and is provided with an annular groove 16 which is connected via a passage 16a with a nipple 18, by means of which it can be connected to a vacuum pump (not shown). Supporting rings 17 (of which one is shown) of different width and height can be inserted into the groove 16, to permit fitment of the measuring means to the tissue to be measured, when the measuring means is placed against the tissue with which it forms a seal due to the suction effect existing in the groove 16.

The embodiment shown in Figure 2 is intended for measurements where indicators are used which can be polarographically determined. In this embodiment, wherein like elements have the same reference numerals as in Figure 1, a unit M is shown having again a surface 10 and having a heating device 12. Here, however, a ring member 30 is provided in which the heating device 12 is mounted, the heating device 12 being connected to the ring member 30 which has the surface 10 in such a manner that good thermal conductivity exists between them. Located within the confines of the ring member 30 is a multiple-wire electrode. It serves to measure the local oxygen pressure and has electrode wires 23, 24, 25 and 26 which are of platinum and have a diameter of approximately 15 microns. The wires 23 to 26 are embedded in a glass body 22 in which the thermal sensor 13 is also secured. The member having the surface 10 serves as a counter electrode, being of silver with a chlorided surface. The entire measuring means is in contact with an electrolyte which may, for instance, be stored in a Cuprophane foil 28 (Cuprophane is a Registered Trade Mark) which is an especially thin cellophane-type foil and is surrounded by a gas-permeable membrane 27, for instance of polytetrafluoroethylene having a thickness of approximately 10 microns, and with sealing means 29.

The electrodes 23, 24 and 26 have small time constants and are advantageously located at the corners of an approximately equilateral triangle. The electrode 25, which serves as a calibrating electrode and has a high time constant for this reason, is located at the middle of the triangle, where the thermal sensor 13 is also located. It should be understood that two-wire electrodes, or electrodes wherein the individual electrode wires are arranged in a different manner than described can also be used.

A surface 31 is to be placed against the diagrammatically illustrated tissue, and annular adhesive strips 32 may be provided on the flange formed with the surface 31 to secure the device temporarily to the tissue. The adhesive members 32 can be constructed as ring members which are adhesively coated on one side, or they can be ring members which are adhesively coated on two sides in which case—contrary to what is shown in Figure 2—they would be located between the tissue and the surface 31 and removably adhere to both of them.

Figures 3 and 3a show the unit M of Figure 2 incorporated in an inflatable pressure-exerting cuff D which can be placed around a human arm which is shown in Figure 3a. Such cuffs are conventional and it will be understood that if air or another gas is admitted via the hose S into the cuff D, the latter will be inflated and exert a pressure upon the arm, locally interrupting the flow of blood so that the extent of skin

breathing can be determined by the time derivative of oxygen pressure, i.e. by the quotient

$$\frac{dPO_2}{dt}.$$

The haemoglobin content can be measured in this manner also. (R. Huch, structural thesis, Marburg 1971, p. 17.)

Referring now to Figure 4, it will be seen that this illustrates a circuit arrangement of part of a device. This circuit arrangement has the advantage that the temperature T_1 of the first surface 10 which is heated by the heating unit H at a constant temperature, and the temperature T_2 of the second surface 13 (i.e., the sensor 13) are both used to form a differential signal I which is proportional to a function of the perfusion. At the same time, a signal C indicative of the indicator concentration, is obtained, for instance from a platinum electrode 23 of the unit M shown in Figure 2. The signals I and C are combined by means not shown to provide a reading indicative of the perfusion efficiency factor of the tissue.

If in certain instances the thermal flow values of the skin can be considered constant, then it is possible to use the "body core temperature" of the human being as a reference temperature. This makes it possible to measure only that amount of heat which must be supplied to maintain an area of the skin at a temperature higher than the body core temperature.

For this reason it is advantageous if, as shown in Figure 5, the surface 10 surrounds a measuring instrument 14a for indicator concentration, so that the instrument 14a is centrally located within the area surrounded by the surface 10. The latter is heated via an electrical regulating device H well known in the art at a constant temperature T_1, and the amount of heat required to maintain the temperature of the surface 10 constant at a selected level is measured by a measuring instrument to obtain a signal I. The amount of heat required to maintain the temperature of the surface 10 constant is proportional to a function of the perfusion, if T_1 is above the body core temperature, the latter being monitored at the same time. The signals I and C are again combined to provide a reading indicative of the perfusion efficiency factor.

Figure 6, finally, shows that it is also advantageous if the signal I corresponding to the perfusion rate is combined electronically in a functional amplifier (well known in the art) with the signal C corresponding to the indicator concentration, to produce a resulting signal

$$E=fe(I.C).$$

A further advantage is obtained if the temperature of the surface 10, that is the temperature T_1, can be varied between 37° and 42°F., either continuously or in steps. It has been found that, during prolonged hyperemia at 42°C., hyperemia is maintained even after the skin is cooled to 37°C., the so-called excess hyperemia. This means that, for instance, the measurement of blood gases can be percutaneously carried out at body temperature. Since the physiological reactions take place without any influence upon them on the part of the measuring device if they are carried out at body core temperature, the danger of measuring errors is eliminated. The continuous measurement of the value I also provides for a control as to when the previously produced hyperemia reverse itself.

Just as in the case using a temperature drop for determining perfusion, advantages are also obtained when the body core temperature is used as a reference temperature, and when the unit 14a is constructed as a multiple-wire platinum electrode for measuring the oxygen pressure, of the type described with reference to Figure 2. For this purpose the embodiment of Figure 5 would require that the member having the surface 10 be of chlorided silver (Ag/AgCl) and have a low heat capacity, surrounding the multiple-wire platinum electrode 14a in an annular manner and being electrically heatable via the regulating arrangement H, with the heat supplied being measured to obtain a signal I. Four platinum electrode wires can be used, as shown in Figure 2, and these platinum electrode wires can be so connected that the electrodes 23, 24 and 26 are connected in parallel with one another because this permits simple summation of the signals of the individual electrodes 23, 24 and 26. A further improvement can be obtained if the electrodes 23, 24 and 26 have a small or low response time, whereas the electrode 25 has a high response time for calibrating purposes, and if the electrodes 23, 24, 26 on the one hand, and the electrode 25 on the other hand can be sequentially connected with the instrument producing the signal I, because this makes it possible to determine if and whether the device has been placed uniformly against the tissue to be measured. This also enables one to control calibration of the device.

WHAT WE CLAIM IS:—

1. A method for determining the perfusion efficiency factor (as hereinbefore defined) of animal tissue, which comprises percutaneously measuring the rate of perfusion of an indicator substance in the tissue at a specified locus and simultaneously measuring the indicator concentration at said locus, signals being obtained in dependence on said

measurements and the signals combined to obtain a composite signal corresponding to said factor.

2. A method according to claim 1 which additionally involves interrupting the circulation of blood through the tissue at said locus and measuring the skin breathing factor of the tissue.

3. A device for use in the percutaneous measurement of the perfusion efficiency factor (as hereinbefore defined) of animal tissue, comprising first means defining a first surface adapted to be placed against the tissue to be measured; second means for producing a controlled temperature in said first means at said first surface; third means for measuring the temperature of said first surface; fourth means defining a second surface surrounded by and located substantially centrally of said first surface; fifth means for measuring the temperature of the tissue at said second surface; and sixth means also surrounded by said first surface and operative for measuring an indicator concentration in said tissue.

4. A device according to claim 3, wherein an inflatable pressure-exerting cuff is provided and is operative for effecting the interruption of blood-circulation through the tissue, said first, second, third, fourth, fifth and sixth means being mounted in said cuff.

5. A device according to claim 3, wherein said second means is regulatable for adjusting the temperature of at least said first surface to a level higher than the skin temperature.

6. A device according to claim 3, wherein said sixth means comprises a plurality of platinum electrodes having respective faces, an electrolyte in operative contact with said faces, and a gas-permeable membrane covering all of said faces; and wherein said first surface is annular and said first means constitutes a counter-electrode for said platinum electrodes.

7. A device according to claim 3, wherein said first surface is annular and is formed with an annular groove and wherein connecting means are provided for connecting said groove to a vacuum pump.

8. A device according to claim 3, wherein adhesive means are provided for removably connecting said device to the tissue being measured, with said first surface contacting said tissue.

9. A device according to claim 3, wherein further means are provided for comparing the temperatures measured by said third and fifth means, and for forming a signal indicating the difference between said temperatures.

10. A device according to claim 3, wherein said second means comprises electric heating means operative to produce a constant temperature of selectable level at said first surface.

11. A device according to claim 10, wherein means are provided for comparing the temperatures measured by said third and fifth means, and for forming a signal indicating the difference between said temperatures; and wherein means are provided for combining said signal with a signal derived from said sixth means to form a composite signal.

12. A device according to claim 6, wherein said first means is composed of Ag/AgCl at least at said first surface and has a low thermal capacity; and wherein said second means comprises electric heating means operative to produce a constant temperature of selectable level at said first surface.

13. A device according to claim 12, wherein said sixth means comprises four platinum electrodes, and wherein said platinum electrodes are connected in parallel with one another.

14. A device according to claim 13, wherein three of said platinum electrodes have a small response time, and wherein one of said platinum electrodes has a large response time and serves as a calibrating electrode.

15. A device according to claim 3, wherein said second means is regulatable for adjusting the temperature of said first surface to between 37° and 42°.

16. A method for determining the perfusion efficiency factor (as hereinbefore defined) of animal tissue substantially as hereinbefore described with reference to the accompanying drawings.

17. A device for determining the perfusion efficiency factor (as hereinbefore defined) of animal tissue substantially as hereinbefore described with reference to the accompanying drawings.

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1461345 COMPLETE SPECIFICATION
2 SHEETS This drawing is a reproduction of the Original on a reduced scale
Sheet 1

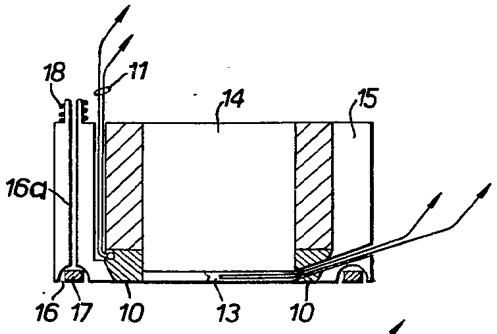

FIG. 1.

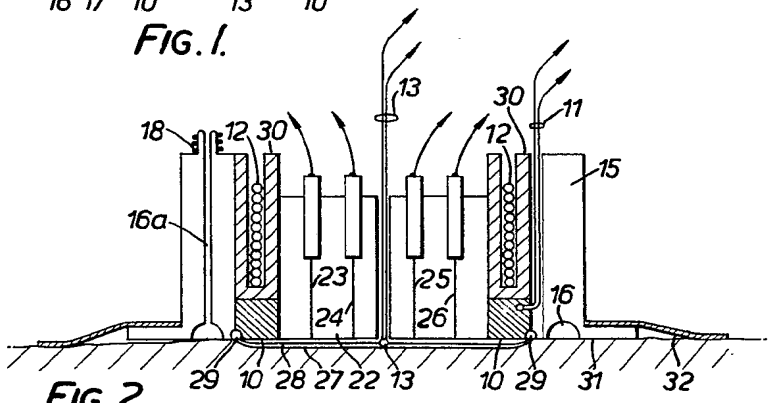

FIG. 2.

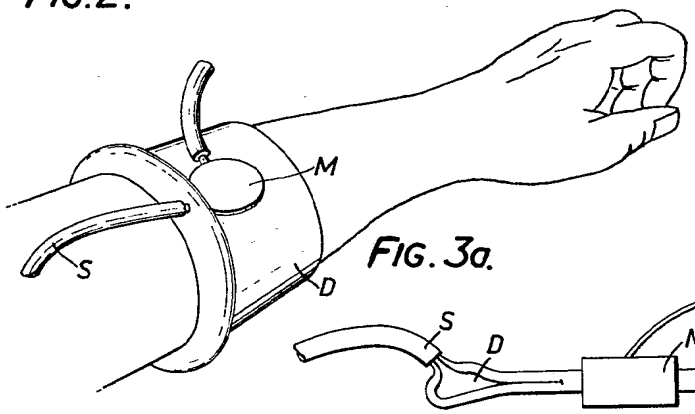

FIG. 3a.

FIG. 3.

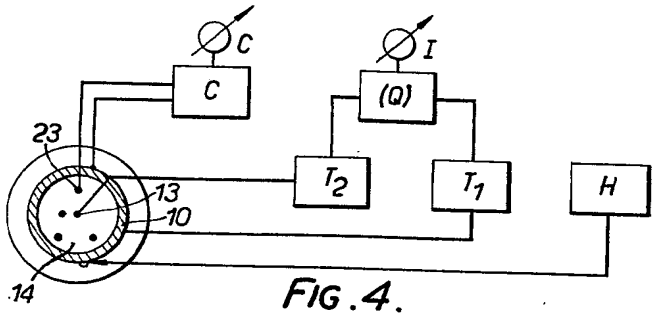

FIG. 4.

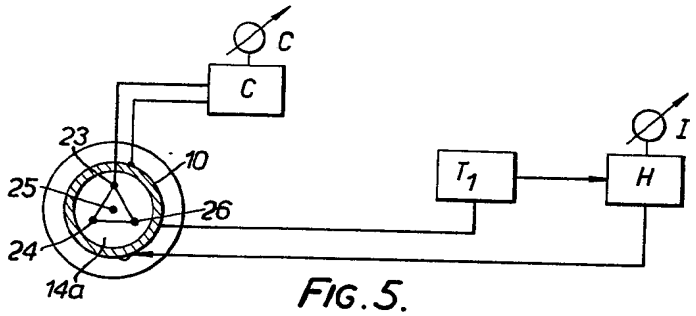

FIG. 5.

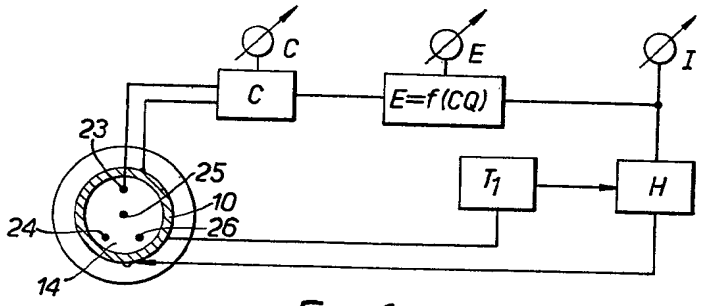

FIG. 6.